

REMARKS

Upon entry of the amendments, claims 1, 3-19, and 21-38 will be pending in the application. Claims 1, 3-5, 7, 9-11, 16, 18, and 19 have been amended and new claims 22-38 added. Support for the amendment to claim 1 appears in the specification at, e.g., page 8, lines 9-10 and the paragraph bridging pages 1 and 2 of the specification (disclosing “polynucleotide”); and page 9, lines 9-15; and page 14, lines 14-16 (disclosing attachment of a separation group only if a targeting element has bound to a target sequence). Claims 3-5, 7, 9-11, 16, 18, and 19 are amended to more particularly point the claimed invention.

Support for new claim 22 appears in previous claims 1, 4-7 (disclosing that the targeting element is an oligonucleotide and the separation group is an immobilizable nucleotide). New claims 23-25 are supported in the specification at, e.g., page 4, lines 12-17. New claim 26 is supported at, e.g., previous claim 1 and page 4, lines 7-8 (disclosing covalent attachment of a separation group). Support for new claims 27-29 is found in the specification at, e.g., page 2, lines 25-26, page 4, lines 7,8,15-17, page 10, lines 26-28, and original claim 9. New claim 30 is supported in the specification by original claims 5, 7 and at page 4, lines 7-8. New claims 31 and 32 are supported in the specification at pages 3, lines 10. New claim 31 is supported in the specification at, e.g., page 13, line 31 to page 14, line 4. New claim 33 is supported in the specification at, e.g., page 13, line 31 to page 14, line 11. New claims 34-35 and 38 are supported by original claims 5 and at page 13, line 31 to page 14, line 4. No new matter is added by these amendments.

New claims 22-25 correspond to claim 1 as amended and further require that the targeting element is an oligonucleotide and that the separation group is an immobilizable nucleotide. New claims 26-29 correspond to previous claim 21 but require that the separation group is covalently attached to the targeting element. New claims 30-32 also require that the separation group is covalently attached to the targeting element and further require that the targeting element is an oligonucleotide and that the separation group is an immobilizable nucleotide.

New claims 33-38 correspond generally to previous claim 1 but require that the targeting element is pre-attached to the separation group, and that the binding of the targeting element-separation group to the target nucleic acid sequence is selectively stabilized in the distinction step.

Rejections under 35 USC § 102

Claims 1, 3-6, 10, 13-16, 18, and 21 are rejected as anticipated under 35 USC § 102(b) by Whitcombe et al., WO97/42345 (“Whitcombe”). The rejection is traversed as applied to these claims as amended and is also addressed with respect to new claims 22-38.

Applicants note the Examiner’s statement in the May 6, 2003 Advisory Action that “the claims are not limited to separating and detecting a nucleic acid present in the starting population”.

Applicants believe the present amendment to independent claim 1, from which the remaining claims subject to the rejection depend, addresses the Examiner’s concerns. The method specified in claim 1 as amended, from which the remaining claims subject to the rejection depend, has been amended to more clearly specify that the polynucleotide removed in the final recited step (now labeled step (e)) is the same polynucleotide of interest specified in step (a) of

the recited method. That is, the removed polynucleotide is present throughout the recited steps, from step (a) through the subsequent contacting, attaching, and immobilizing steps (steps (b)-(d)).

In contrast, the method described in Whitcombe does not result in the isolation and detection of the actual polynucleotide of interest itself from a starting population of nucleic acid molecules. Instead, Whitcombe describes a method in which a series of extension products are prepared. The first extension product is generated from a diagnostic primer that includes a tail sequence with a tag region and a detector region (see page 1, line 28-page 2, line 4). The extension product then acts as a template for the extension of a further primer that hybridizes to a locus at a distance from the diagnostic base sequence; the further primer when extended forms a further extension product (page 2, lines 5-10; see also claim 1). The presence or absence of a diagnostic base sequence is detected by reference to a detector region in the further extension product using methods discussed at page 2, line 11, to page 3, line 6 and claims 2-6.

Thus, Whitcombe describes a method that detects not the starting polynucleotide of interest itself but instead an amplification product whose synthesis is dependent on the presence of a sequence of interest. For this reason, this reference does not describe the invention of claim 1 and its dependent claims, claims 3-6, 10, 13-16, 18, and 21.

New claim 22 corresponds to previous claim 21, along with previous claims 4-7. Claim 7 is not subject to the rejection for anticipation by Whitcombe. Therefore, new claim 22, along with its dependent claims 23-25, and new claims 30-32, are not described by this reference.

New claims 26-29 require that the separation group be covalently attached to the targeting element. This feature distinguishes the claimed invention from Whitcombe, which describes a method in which a detector species (corresponding to Applicants' separation group; see page 6,

first paragraph of the December 19, 2002 Office Action) associates non-covalently with a detector region in an nucleic acid sequence element termed a “further extension product” (corresponding to Applicants’ targeting element).

New claims 33-36 require that the targeting element contacts the polynucleotide of interest with the separation group already attached; and that the targeted / immobilized polynucleotide of interest is present from the outset. Whitcombe also fails to describe this feature of the claimed invention (see also page 2, lines 22 in Whitcombe, which specifically excludes "other nucleic acid sequences in the sample").

Claims 1, 3-15, 17, 18, and 21 are rejected as anticipated under 35 USC § 102 (e) by Lundeberg et al., US Patent No. 6,482,592 (“Lundeberg”). The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner states in the May 6, 2003 Advisory Action that “the claims do not recite limitations wherein the attachment of the separation groups is indispensable to the presence of the bound targeting element and distinguishing element in the vicinity of the bound targeting element.”

To address the Examiner’s concern, all of the pending claims now specify that attachment of the separation group occurs only if the targeting element is bound to a target sequence on the polynucleotide of interest.

Lundeberg does not describe this feature of the claimed invention. The Examiner states that the modular oligonucleotide described in Lundeberg corresponds to a targeting element, and that a modulating module/capture probe corresponds to a separation group (page 8, second paragraph of the Office Action). Lundeberg teaches that binding of the modular oligonucleotide - which includes "at least two modules", or parts (column 1, line 59; and column 6, line 51) - is

improved relative to a single oligonucleotide through the mutual interaction of the two adjacent modules, i.e. the further module / modulator and the capture / detection module (column 6, lines 42-45) . However, the binding of neither the "further module / modulator" ('targeting element') nor of the "capture / detection module" ('separation group') is a necessary prerequisite for binding of the other module. Each part of the modular oligonucleotide is itself a single oligonucleotide of significant length (column 1, line 64; Figs. 3A and 3B) and will bind to the target nucleic acid molecule even in the complete absence of the other, albeit at a decreased efficiency due to the absence of the effect described here. . Thus, Lundeborg does not describe a method in which attachment of the separation group ('capture / detection module') occurs only if the targeting element ('further module / modulator') is bound to a target sequence on the polynucleotide of interest in the presence of a distinguishing element in its vicinity, and so fails to anticipate the invention of claim 1 and claims depending from claim 1.

In view of the foregoing comments, Applicants respectfully request reconsideration and withdrawal of the rejections for anticipation.

Rejections under 35 USC § 103(a)

Claim 16 is rejected as unpatentable over Lundeborg in view of Whitcombe. The rejection is traversed.

Claim 16 depends from claim 1 and further requires that the distinguishing element is a single nucleotide polymorphism. As is explained above, Lundeborg does not make obvious the invention of claim 1 because it discloses oligonucleotides as targeting elements and separation groups. Binding of the oligonucleotides is not obligatory, but instead is, according to Lundeborg, enhanced when both oligonucleotides are present. Lundeborg neither discloses nor suggests any

separation groups that bind only if the targeting element is bound to a target sequence on the polynucleotide of interest and if a distinguishing element is present in the vicinity.

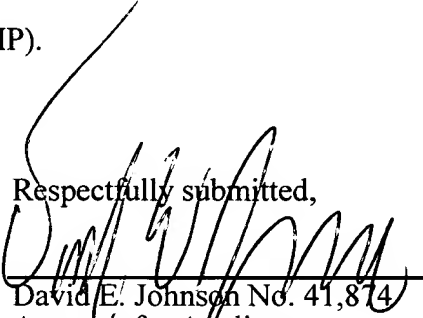
Whitcombe is used to complete the rejection by teaching the identification of single nucleotide polymorphisms. However, it, fails to disclose or suggests a separation group that binds only if a distinguishing element and a bound targeting element are present in the vicinity nucleic of a acid sequence of interest, and wherein the nucleic acid sequence of interest is present in a provided population of nucleic acid molecules (see first recited step), as well as during the subsequent contacting, attaching, and immobilizing steps. Thus, claim 1 is non-obvious over the combination of Lundeberg and Whitcombe. Because claim 16 depends from claim 1, it too, is non-obvious over the combination of Lundeberg and Whitcomb. Therefore, the cited references do not render claim 16 *prima facie* obvious.

Claim 19 has been rejected as obvious over Lundeberg. The rejection is traversed. Claim 19 is drawn to a method in which removal of the separation group occurs only if the distinguishing element in the vicinity of the bound targeting element is absent. There is no suggestion in Lundeberg of a method with this step. Therefore, claim 19 is not *prima facie* obvious over this reference, and Applicants respectfully request reconsideration and withdrawal of the rejections for obviousness.

A petition for extension of time and request for continued examination accompany this response. The Commissioner is hereby authorized to charge payment of any fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 22650-001CIP).

13 NOVEMBER 2003

Respectfully submitted,


David E. Johnson No. 41,874
Attorney for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

TRA 1850783v1

TRA 1850783v2